BCS, IT'S SIGNIFICANCE AND APPLICATION

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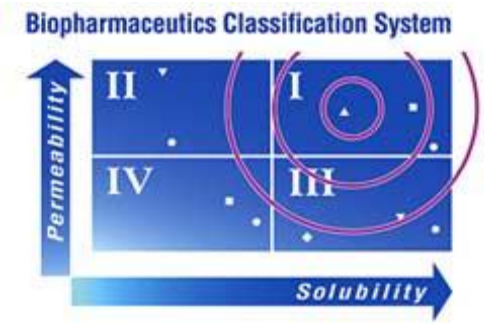
The Biopharmaceutics Classification System

Introduction:-

- ✓ The oral route of drug administration is the route of choice for the formulators and continues to dominate the area of drug delivery technologies. However, though popular, this route is not free from limitations of absorption and bioavailability in the milieu of gastrointestinal tract.
- ✓ Whenever a dosage form is administered orally, the events that follow are depicted in Figure1. The drug in the dosage form is released and dissolves in the surrounding gastrointestinal fluid to form a solution. This process is solubility limited.
- ✓ Once the drug is in the solution form, it passes across the membranes of the cells lining the Gastro-Intestinal tract. This process is permeability limited. Then onwards the drug is absorbed into systemic circulation. In short, the oral absorption and hence bioavailability of drug is determined by the extent of drug solubility and permeability.
- ✓ The BCS is a scientific framework for classifying drug substances based on their aqueous solubility as related to dose and intestinal permeability.
- ✓ When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: ***dissolution, solubility, and intestinal permeability***.

The objective of the BCS is : to *predict in vivo performance of drug products from in vitro measurements of permeability and solubility.*

According to the BCS, drug substances are classified as follows:



Class 1: High Solubility - High Permeability

Class 2: Low Solubility - High Permeability

Class 3: High Solubility - Low Permeability

Class 4: Low Solubility - Low Permeability

Class I drugs exhibit a **high absorption number and a high dissolution number**. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step.Rate of absorption is higher than rate of excretion. e.g. Metoprolol, Diltiazem, Verapamil, Propranolol.

Class II drugs have a **high absorption number but a low dissolution number**. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. The absorption for class II drugs is usually slower than class I and occurs over a longer period of time. In vitro- In vivo correlation (IVIVC) is usually excepted for class I and class II drugs. e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine.

For **Class III** drugs, permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. e.g. Cimetidine, Acyclovir, Neomycin B, Captopril.

Class IV drugs exhibit a lot of problems for effective oral administration. Fortunately, extreme examples of class IV compounds are the exception rather than the rule and are rarely developed and reach the market. Nevertheless a number of class IV drugs do exist. e.g. Taxol, Griseofulvin.

Note:

- Absorption no is ratio of mean residence time to mean absorption time.
- Dissolution no is ratio of mean residence time to mean dissolution time

Aim of BCS Guidance:

- To improve the efficiency of drug development and the review process by recommending a strategy for identifying expendable clinical BE tests.
- To recommend methods for classification according to dosage form dissolution along with the solubility , permeability characteristics of the drug product.

- To provide regulatory tool for replacing certain bioequivalence studies by accurate in-vitro dissolution tests.
- This will reduce the cost in drug development process ,also reduce unnecessary drug exposure in healthy objects.
- To provide guidance for industry.

	High Solubility	Low Solubility
High Permeability	**Class 1** Abacavir Acetaminophen *Acyclovir*[b] *Amiloride*[S,I] Amitryptyline[S,I] Antipyrine *Atropine* **Buspirone**[c] Caffeine *Captopril* Chloroquine[S,I] **Chlorpheniramine** Cyclophosphamide Desipramine **Diazepam** **Diltiazem**[S,I] **Diphenhydramine** Disopyramide **Doxepin** Doxycycline Enalapril Ephedrine Ergonovine Ethambutol Ethinyl Estradiol Fluoxetine[I] Glucose Imipramine[I] **Ketorolac** Ketoprofen Labetolol Levodopa[S] Levofloxacin[S] **Lidocaine**[I] Lomefloxacin **Meperidine** Metoprolol Metronidazole **Midazolam**[S,I] **Minocycline** Misoprostol **Nifedipine**[S] Phenobarbital Phenylalanine Prednisolone **Primaquine**[S] Promazine Propranolol[I] **Quinidine**[S,I] Rosiglitazone Salicylic acid Theophylline Valproic acid **Verapamil**[I] Zidovudine	**Class 2** **Amiodarone**[I] **Atorvastatin**[S, I] **Azithromycin**[S ,I] **Carbamazepine**[S,I] **Carvedilol** Chlorpromazine[I] **Cisapride**[S] *Ciprofloxacin*[S] **Cyclosporine**[S, I] **Danazol** **Dapsone** Diclofenac Diflunisal Digoxin[S] *Erythromycin*[S,I] Flurbiprofen **Glipizide** **Glyburide**[S,I] Griseofulvin Ibuprofen **Indinavir**[S] Indomethacin **Itraconazole**[S,I] **Ketoconazole**[I] **Lansoprazole**[I] **Lovastatin**[S,I] *Mebendazole* Naproxen Nelfinavir[S,I] Ofloxacin Oxaprozin Phenazopyridine Phenytoin[S] Piroxicam Raloxifene[S] **Ritonavir**[S,I] **Saquinavir**[S,I] **Sirolimus**[S] Spironolactone[I] **Tacrolimus**[S,I] Talinolol[S] **Tamoxifen**[I] **Terfenadine**[I] Warfarin

	High Solubility	Low Solubility
Low Permeability	**Class 3** *Acyclovir* *Amiloride*[S,I] Amoxicillin[S,I] Atenolol *Atropine* Bisphosphonates Bidisomide *Captopril* Cefazolin Cetirizine Cimetidine[S] *Ciprofloxacin*[S] Cloxacillin Dicloxacillin[S] *Erythromycin*[S,I] Famotidine Fexofenadine[S] Folinic acid *Furosemide* Ganciclovir *Hydrochlorothiazide* Lisinopril Metformin *Methotrexate* Nadolol Pravastatin[S] Penicillins Ranitidine[S] Tetracycline Trimethoprim[S] Valsartan Zalcitabine	**Class 4** Amphotericin B Chlorthalidone Chlorothiazide Colistin *Ciprofloxacin*[S] *Furosemide* *Hydrochlorothiazide* *Mebendazole* *Methotrexate* Neomycin

Basic Requirements of BCS:

- It must predict the *in-vivo* dissolution system well.
- Rate limiting step for *in-vivo* absorption must be well defined.
- Limits for permeability and solubility must be balanced.
- *In-vitro* methods should be sufficiently robust for correct classification.

Serious Limitations of BCS:

- Absorption transporters and efflux pumps are not considered.
- Drugs undergoing first pass metabolism or secondary metabolism are not factored in appropriate manner.
- Solubility and permeability measurements are loosely defined.
- Food effect is not considered.
- Chances of misclassification.
- It is based on highest dose but..(what about smaller doses of same product?)
- Intended only for immediate release(IR) products that are absorbed throughout GIT.

Class Boundaries:

- A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in $\leq$ 250 ml water over a pH range of 1 to 7.5.
- In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered HIGHLY PERMEABLE when the extent of absorption in humans is determined to be $\geq$ 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.
- In this guidance, an IR drug product is considered RAPIDLY DISSOLVING when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using *U.S. Pharmacopeias* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media:
- (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes;
- (2) a pH 4.5 buffer;
- (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

Possibilities of shifting the solubility – dissolution characteristics form a very poorly soluble drug to D.S within the range of values encountered in the Human GI tract.

- e.g.Solubilization & Stabilization of **Na-DICLOXACILLIN** by ***pH*** and ***CD Inclusion Complexation*.**
- Enhanced solubility & dissolution rate of **LAMOTRIGINE** by inclusion **Complexation** with β-CD **To increase aqueous solubility of drugs.**
  e.g. Solubility enhancement of **NITROBENZAMIDE** in aq solution by **β-CD** for cancer treatment.
- **To increase permeability of drugs.**
  e.g. Assessment of **METHYL SULFONYL METHANE** as a permeability enhancer for regional **EDTA** chelation therapy.

Biopharmaceutic Classification System Of β-blockers:

- Seven β-Blockers were studied for their solubility & permeability.
- Labetalol, Timolol, Metoprolol → Class-I
- Acebutolol,Atenolol,Nadolol → Class-III
- All β-Blockers showed consistent permeability with reported extent of intestinal permeability except Sotalol & this might be due to its low lipophilicity.
- In addition, Difference between tightness of intercellular junction *in-vivo* & *in-vitro* may contribute to this display in Sotalol permeability. (Chemical Abstract,vol.147(7),Aug-2007)

Solubility Determination:

1. pH-solubility profile of test drug in aqueous media with a pH range of 1 to 7.5.
2. Shake-flask or titration method

- ♣ The pH-solubility profile of the test drug substance should be determined at 37 ± 1^{o}C in aqueous media with a pH in the range of 1-7.5. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance.
- ♣ Solubility should be determined at pH = p Ka, pH = p Ka +1, pH = pKa-1, and at pH = 1 and 7.5. A minimum of three replicate determinations of solubility in each pH condition is recommended. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies.
- ♣ Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance.
- ♣ Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products.

Permeability Determination:

Extent of absorption in humans:

- Mass-balance pharmacokinetic studies.

In mass balance studies, unlabelled, stable isotopes or radiolabelled drug substances are used to determine the extent of drug absorption. However this method gives highly variable estimates and hence other methods are sought for.

- Absolute bioavailability studies

In absolute bioavailability studies, oral bioavailability is determined and compared against the intra venous bioavailability as reference.

Intestinal permeability methods:

- *In vivo* intestinal perfusions studies in humans.
- *In vivo* intestinal perfusion studies in animals.
- *In vitro* permeation experiments with excised human or animal intestinal tissue.
- *In vitro* permeation experiments across epithelial cell monolayers.

- Intestinal perfusion models and in vitro methods are recommended for passively transported drugs. The observed low permeability of some drug substances in human could be attributed to the efflux of drug by various membrane transporters like p-glycoprotein. This leads to misinterpretation of the permeability of drug substance.
- The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods).
- In many cases, a single method may be sufficient (e.g., when the absolute BA is 90% or more, or when 90% or more of the administered drug is recovered in urine). When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable.
- An interesting alternative to intestinal tissue models is the use of well-established in vitro systems based on the human adenocarcinoma cell line Caco-2. These cells serve as a model of small intestinal tissue. The differentiated cells exhibit the microvilli typical of the small intestinal mucosa and the integral membrane proteins of the brush-border enzymes. In addition, they also form the fluid-filled domes typical of a permeable epithelium. Recent investigations of Caco-2 cell lines have indicated their ability to transport ions, sugars and peptides. The directed transport of bile acids and vitamin B12 across Caco-2 cell lines has also been observed. These properties have established the Caco-2 cell line as a reliable in vitro model of the small intestine.
- The most common in-vitro cell culture technique used to assess permeability is the CaCo –2 (human colon carcinoma) cell live & / or sub-clone (e.g. Tc-7) based estimates.

Determining dissolution profile similarity:

- For capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.
- The USP Apparatus I (*basket method*) is generally preferred for capsules and products that tend to float, and USP Apparatus II (*paddle method*) is generally preferred for tablets.
- For some tablet dosage forms, in vitro (but not in vivo) dissolution may be slow due to the manner in which the disintegrated product settles at the bottom of a dissolution vessel. In such situations, USP Apparatus I may be preferred over Apparatus II.

- If the testing conditions need to be modified to better reflect rapid in vivo dissolution (e.g., use of a different rotating speed), such modifications can be justified by comparing in vitro dissolution with in vivo absorption data (e.g., a relative BA study using a simple aqueous solution as the reference product).
- **A minimum of 12 dosage units** of a drug product should be evaluated to support a biowaiver request.
- When comparing the test and reference products, dissolution profiles should be **compared using a similarity factor (f_2).** The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.
- Two dissolution profiles are considered similar when the f_2 value is _50. To allow the use of mean data, the coefficient of variation should not be more than 20% at the earlier time points (e.g., 10 minutes), and should not be more than 10% at other time points.
- Note that when both test and reference products dissolve 85% or more of the label amount of the drug in _15 minutes using all three dissolution media recommended above, the profile comparison with an f_2 test is unnecessary.

Biowaivers:

Bioequivalence study may be replaced by in vitro dissolution testing**.** When such a substitution is allowed by registration authorities this is referred to as a **"biowaiver".**

Conditions for justifying request of biowaiver .

1. Drug must be highly soluble & permeable.
2. Must be stable in GIT.
3. Product is designed not to be absorbed in oral cavity.
4. Must not have narrow therapeutic index.
5. Excipients used in IR solid dosage forms must have no significant effect on rate & extent of oral drug absorption .

ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIOWAIVER

When requesting a BCS-based waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors can affect their request or the documentation of their request:

A. Excipients

- In general, using excipients that are currently FDA-approved in IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product.
- To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage

form, additional information documenting the absence of an impact on BA of the drug may be requested by the Agency. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product.

B. Prodrugs

- Permeability of prodrugs will depend on the mechanism and (anatomical) site of conversion to the drug substance. When the prodrug-to-drug conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and pH-solubility data on both prodrug and drug can be relevant

BIOWAIVER EXTENSIONS:

(1) For class II drugs:

- Here *in-vivo* dissolution is rate limiting step.
- If *in-vivo* dissolution can be estimated in vitro, it is possible to establish *IVIVC*. But experimental methods are difficult to design & validate because no. of *in-vitro* process involved.
- Key determinant for class II drug absorption is the solubility in the absorbing region of intestine.
- So, change in formulation is required.
- Add SLS to mimic solubilization in vitro and maintenance of sink condition in vivo resulting from continuous absorption.
- Addition of various surfactants concentration in dissolution media may be adequate for quality control but not sufficient for predicting *in-vivo* dissolution.

(2) For class III drugs:

- Drugs shows permeability limited absorption
- It has been contended that there are equally compelling reasons to grant biowaivers to class III drugs as class I drugs.
- If the dissolution of class III drugs is rapid under all physiological pH conditions, it is expected that they will behave like oral solution *in-vivo* and *in-vivo* bioequivalence study is generally waived off for oral solutions.
- Recent survey of FDA data of over 10 BCS class III drugs shows that most commonly used excipients in oral solid dosage forms have no significant effect on absorption.
- Class III drug products containing significant amount of GIT transit affecting or permeability changing excipient should be excluded from consideration of biowaivers.
- For E.g. **SLS, fatty acids, steroidal detergents** changes membrane permeability. **Mannitol, sorbitol** can reduce small intestine transit time.
- **Isoniazid** which lies at borderline of BCS class I & III. Its biowaiver is recommended when the test product meets WHO requirements for “Very rapidly dissolving” and

contains only excipients commonly used in isoniazid products . Lactose & other deoxidizing saccharides containing formulations should be subjected to *in-vivo* BE study.

Drugs whose Biowaiver Study have been tried:

- Metoclopramide(Class-III)
- Acetazolamide(Class-IV)
- Pyrizinamide(Class-III)
- Ethambutol(Class-III)

Biowaiver Monographs for IR oral solid Dosage Forms:

- **QUINIDINE SULPHATE:**
  Highly soluble and moderately to highly permeable (Class I or at worst Class III).Solubility data is incomplete and data on permeability is based on in-vitro models which are not adequate. Due to narrow therapeutic index and critical indication biowaiver based approval can not be recommended

- **RIFAMPICIN:**
  BCS Class II drug. Narrowly misses solubility requirements due to wettability problem. No reports were identified in which in vitro dissolution was shown to be predictive of non-equivalence among products. Biowaiver approval is not recommended for major scale up and post approval changes.

- **DICLOFENAC:**
  BCS ClassII drug.Biowaiver can be recommended.
  Because :
  Test and comparator contain same diclofenac salt.DF of test and comparator are identical.Excipients used were approved in ICH.both dissolve 85% in 30min or less in 900ml buffer of pH 6.8 using paddle appratus at 75rpm or basket appratus at 100rpm.dissolution profile similarity at pH 1.2, 4.5, 6.8 .

Industrial Implementation of the BCS:

Introduction

In 1995 Amidon et al. devised a bio-pharmacetics classification system (BCS) to classify drugs based on their aqueous solubility and intestinal permeability. It was then recognized that dissolution rate has a negligible impact on bioavailability of highly soluble and highly permeable (BCS Class I) drugs when their formulation's dissolution is sufficiently rapid. As a result, various regulatory agencies including the United States Food and Drug Administration (FDA) now allow bioequivalence of formulations of BCS Class I drugs to be demonstrated by in vitro dissolution (often called a bio-waiver).

Potential Cost Savings.

- The potential savings is a function of the potential number and likely cost of bioequivalence studies saved (not performed).
- To examine the potential savings, the number of bioequivalence studies performed by the pharmaceutical industry per year was examined. Thus, it is estimated that the pharmaceutical industry spends between 90 and 150 million dollars a year on bioequivalence studies.
- Approximately 25% of all compounds were classified as highly soluble and permeable with approximately another 41% having insufficient data to allow classification.
- Using the 25% estimated, there is the potential to save one quarter the annual expenditures on bioequivalence studies, $22 to $38 million dollars/year. Additional indirect savings can occur if bioequivalence studies are rate limiting to drug development.
- For example, suppose that results of a bioequivalence study are needed before proceeding with development of a compound with eventual peak sales of one billion dollars/year. It is reasonable to assume that results of in vitro dissolution can be obtained 6 weeks earlier than results from an in vivo bioequivalence trial. This time savings translates into a potential additional $110 million dollars in sales from a 6 week earlier approval. Further, by not having to run a human bioequivalence trial, clinical resources are freed to be applied elsewhere.

REGULATORY APPLICATIONS OF THE BCS:

The widespread use of BCS in pharmaceutical field is partly due to its inclusion in various guidance documents as cited below.

A. INDs / NDAs. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles. This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class I), and the formulations pre- and postchange are *pharmaceutical equivalents*. BCS-based biowaivers are intended only for bioequivalence (BE) studies. They do not apply to food effect bioavailability (BA) studies or other pharmacokinetic studies.

B. ANDAs. BCS-based biowaivers can be requested for rapidly dissolving immediate release (IR) test products containing highly soluble and highly permeable drug substances, provided that the reference listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference listed drug product. This approach is useful when the test and reference dosage forms are pharmaceutical equivalents.

C. Post approval Changes BCS-based biowaivers can be requested for significant post approval changes (e.g., Level 3 changes in components and composition) to a rapidly dissolving immediate release (IR) product containing a highly soluble, highly permeable drug substance, provided that dissolution remains rapid for the

postchange product and both pre- and postchange products exhibit similar dissolution profiles.

- BE studies are presently being conducted for NDA of new drug, ANDA of generic products, scale up & post approval changes.
- BCS is a simple tool in early drug development to determine the rate limiting step in oral absorption process.
- In future, this increased awareness of proper biopharmaceutical characterization of a new drug may result in drug molecules with a sufficiently high solubility, permeability & dissolution that will automatically increase the importance of BCS as a regulatory tool.

SUGGESTED IMPROVEMENTS OF BCS:

BCS could be reduced into two classes.

- **Class-I Permeation rate limited absorption:** Drugs with *in-vivo* K_{diss} > *in-vivo* K_{pe} belong to class I regardless f_a.
- **Class-II Dissolution rate limited absorption:** Drugs with *in-vivo* K_{diss}< *in-vivo* K_{pe} belong to class II. Here in-vivo BE studies are required.

BCS CONTAINING SIX CLASSES:

Bergstrom *et al*. carried out a study, in which ***BCS containing six Classes*** was used, according to which solubility was classified as "high" or "low" and permeability was classified as "low", "intermediate" or "high".

This new classification was given based on correlations between the calculated molecular surface area descriptors, on one hand, and solubility and permeability, on the other. Surface areas related to the non-polar part of the molecule resulted in good predictions of solubility, whereas surface areas describing the polar parts of the molecule resulted in good predictions of permeability. The established correlations were used to perform a theoretical biopharmaceutical classification of WHO listed drugs into six classes, resulting in **a correct prediction for 87% of the essential** drugs.

THIRD DIMENSION TO BCS:

Gohel has suggested that, since living body is a highly chiral environment. So, once the drug meant for oral use dissolves in gastro intestinal fluid and subsequently permeates through the membrane, it enters into general circulation. The drug may under go chiral conversion in blood. Therefore, in such cases, the pharmacological action will depend upon the amount of unchanged active enantiomer reaching the receptors.

So, we can add a third dimension was added to BCS, i.e. chiral conversion for the drugs where only one form (R or S) is active and the other form is inactive. The drugs that fall under Class IB will show superior action as compared to Class IA.

Class	Solubility	Permeability	Chiral Conversion *
I	High	High	A High*
			B Low*
II	Low	High	A High
			B Low
III	High	Low	A High
			B Low
IV	Low	Low	A High
			B Low

*Chiral Conversion- an active form of drug is converted into an inactive form in blood stream. For racemic drugs, the fraction of dose of active enantiomer reaching the receptor site is more relevant for pharmacological response.

*High- higher amount of active enantiomer is converted to inactive form.

*Low- lower amount of active enantiomer is converted to inactive form.

QUANTITATIVE VERSION OF BCS TERMED AS QBCS:

- Experience gained with intensive experiments has shown that the process of dissolution can be dependent on the amount of drug present at the site of absorption (dose), in addition to the solubility of drug in the dissolution fluid.
- It was argued and demonstrated (Rinaki *et al.* 2003) that solubility is a static equilibrium parameter and cannot adequately describe the dynamic character of the dissolution process for the entire dose administered.
- Hence, a single solubility value is inadequate for the purpose of biopharmaceutical classification, because the drugs are administered in various doses; therefore, the dose consideration should be taken into account. This is also emphasized in the FDA guidance for the industry, "Waiver of *in vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutic Classification System," which states that the highest dose strength of an immediate release product should be considered for study.
- Rinaki *et al.* dealt the biopharmaceutical system in a quantitative manner, relying on the central role of dose/solubility ratio for the absorption phenomenon in conjunction with the mean time concept for dissolution, transit, and uptake of the drug in the intestine. These considerations led to the development of the quantitative version of BCS, termed quantitative bcs0 (QBCS).
- The QBCS relies on a (permeability, dose/solubility ratio) plane with cutoff points 2×10^{-6} cm/s to 2×10^{-5} cm/s for permeability and 0.5 to 1.0 for the dose

solubility ratio. Permeability estimates, (P_{app} that is the apparent permeability) were derived from Caco-2 cell studies and a constant intestinal volume content of 250 ml was used to express the dose solubility ratio as a dimensionless quantity (q).

Drugs are classified into four quadrants of a plane, around the cutoff points, according to their P_{app} , and q values, establishing four categories, that is,

I. ($P_{app} > 10^{-5}$ cm/s, $q \leq 0.5$),

II. ($P_{app} > 10^{-5}$ cm/s, $q > 1$),

III. ($P_{app} < 2 \times 10^{-6}$ cm/s, $q \leq 0.5$), and

IV. ($P_{app} < 2 \times 10^{-6}$ cm/s, $q > 1$)

A region of borderline drugs ($2 \times 10^{-6} < P_{app} < 10^{-5}$ cm/s, $0.5 < q < 1.0$) has also been defined.

- For category I, complete absorption is anticipated, whereas, categories II and III exhibit dose/solubility ratio - limited and permeability -and limited absorption, respectively. For category IV both permeability and dose/solubility ratio control drug absorption.
- **Rinaki *et al.*** developed a **quantitative version of BCS termed as QBCS using** the **dose/solubility ratio** as the key parameter for solubility classification .The QBCS utilizes a solubility /dose ratio, permeability plane with scientifically–physiologically based cut-off values for compound classification.

	P*app**(cm/sec)	q*
Class-I	P*app*>10^{-5}cm/sec	q≤ 0.5
Class-II	P*app*>10^{-5}cm/sec	q>1
Class-III	P*app*<2 C 10^{-6}cm/sec	q ≤ 0.5
Class-IV	P*app*<2 C 10^{-6}cm/sec	q.>1

*Papp- apparent permeability and q- Dose/solubility

Conclusion:

- The *in vivo* pharmacokinetics of drugs depends largely on the solubility and permeability.
- The BCS has proven to be an extremely useful **guiding tool for the prediction of the *in vivo* performance** of drug substance and **development of new drug delivery** systems to suit the performance of the drug in the body, as also for the **regulation of bioequivalence** of the drug product during scale-up and post approval.
- In the future, the BCS concept will probably be used increasingly **in the early development** of new drugs, including for analog selection as well as for initial formulation approaches.

Refernces:

- Guidance for Industry "Waiver of In vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on BCS"
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